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Risk factors for unfavourable postoperative outcome in patients with Crohn's disease undergoing right hemicolectomy or ileocaecal resection an international audit by ESCP and S-ECCO

Horisberger, Karoline ; et al

Abstract: Background: Patient and disease-related factors, as well as operation technique all have the potential to impact on postoperative outcome in Crohn's disease. The available evidence is based on small series and often displays conflicting results. Aim: To investigate the effect of pre- and intra-operative risk factors on 30-day postoperative outcome in patients undergoing surgery for Crohn's disease. Method: International prospective snapshot audit including consecutive patients undergoing right hemicolectomy or ileocaecal resection. This study analysed a subset of patients who underwent surgery for Crohn's disease. The primary outcome measure was the overall Clavien-Dindo postoperative complication rate. The key secondary outcomes were anastomotic leak, re-operation, surgical site infection and length of stay at hospital. Multivariable binary logistic regression analyses were used to produce odds ratios (OR) and 95% confidence intervals (CI). Results: Three hundred and seventy five resections in 375 patients were included. The median age was 37 and 57.1% were female. In multivariate analyses, postoperative complications were associated with preoperative parenteral nutrition (OR 2.36 95% CI 1.10-4.97), urgent/expedited surgical intervention (OR 2.00, 95% CI 1.13-3.55) and unplanned intraoperative adverse events (OR 2.30, 95% CI 1.20-4.45). The postoperative length of stay in hospital was prolonged in patients who received preoperative parenteral nutrition (OR 31, CI [1.08-1.61]) and those who had urgent/expedited operations (OR 1.21, CI [1.07-1.37]). Conclusion: Preoperative parenteral nutritional support, urgent/expedited operation and unplanned intraoperative adverse events were associated with unfavourable postoperative outcome. Enhanced preoperative optimization and improved planning of operation pathways and timings may improve outcomes for patients.

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**Risk factors for unfavourable postoperative outcome in patients
with Crohn's disease undergoing right hemicolectomy or ileocaecal
resection**

An international audit by ESCP and S-ECCO.

2015 European Society of Coloproctology collaborating group*

**collaborating members shown in Appendix*

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Results: Three hundred and seventy five resections in 375 patients were included. The median age was 37 and 57.1% were female. In multivariate analyses, postoperative complications were associated with preoperative parenteral nutrition (OR 2.36 95% CI 1.10-4.97)], urgent/expedited surgical intervention (OR 2.00, 95% CI 1.13-3.55) and unplanned intraoperative adverse events (OR 2.30, 95% CI 1.20-4.45). The postoperative length of stay in hospital was prolonged in patients who received preoperative parenteral nutrition (OR 31, CI [1.08-1.61]) and those who had urgent/expedited operations (OR 1.21, CI [1.07-1.37]).

Conclusion: Preoperative parenteral nutritional support, urgent/expedited operation and unplanned intraoperative adverse events were associated with unfavourable postoperative

outcome. Enhanced preoperative optimization and improved planning of operation pathways and timings may improve outcomes for patients.

Keywords: Crohn's disease, surgery, resection, postoperative complications, outcome, parenteral nutrition

What does this paper add to the literature?

We describe the first international prospective multicentre study to collect contemporaneous data on this challenging patient cohort. Much of the literature to date consists of small and retrospective series, often from single centres. We identified the common risk factors associated with unfavourable postoperative outcome and made suggestions for potential pathway improvements like better timing of surgical intervention and preoperative optimization.

Introduction

The postoperative outcome of surgery for Crohn's disease (CD) may be affected by patient, disease, surgical technical, and other perioperative risk factors. Retrospective observational studies have identified several patient-related and disease-related risk factors, including body mass index (1), smoking (2), preoperative intra-abdominal abscess or enteric fistula (3), preoperative albumin (4–6), anaemia (7,8), malnutrition (9,10), and preoperative medical treatment (11–13).

Surgeon and surgery related risk factors might also be crucial to outcome. The rate of first-time intestinal resection in CD is 29.1 % while the 7-year cumulative risk is 28.5 % (14).

Surgery in CD patients remains challenging in terms of timing (15), preoperative

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optimization (8,16,17), and techniques (18). Many of the suspected risk factors are somewhat controversial, including surgeon's grade of specialization (19), preoperative optimization (8), urgency of surgical intervention (15), use of defunctioning ileostomy (20), and method of access to abdominal cavity (21). Anastomosis type and configuration have also been debated without robust evidence to support one type or another to date (22,23). The same applies for skin closure technique, which has been investigated in obstetrics (24) and orthopaedic (25) surgical wounds but not in CD patients.

The quality of evidence supporting the previously described risk factors is low in the majority of studies due to small sample size and their retrospective nature. There is need for a prospective multicentre study with a large sample size. Our was to investigate the effect of patient, disease and surgery related risk factors on the 30-day postoperative outcome in CD patients undergoing right hemicolectomy or ileocaecal resection.

Methods

Study design

A prospective, multicentre, international snapshot audit of patients undergoing elective or emergency right hemicolectomy or ileocaecal resection over a two-month period (mid-January –mid-March 2015). Patients were followed-up for 30 days after the primary operation. The audit was performed according to a pre-specified protocol (<http://www.escp.eu.com/research/cohort-studies/2015-audit>). The methods used were explained in the recently published primary report from the main study (26). This study, including only patients undergoing surgery to treat CD, comprises a pre-specified subgroup analysis.

Objectives

Our aim was to investigate patient and surgery related risk factors that might affect postoperative outcome in CD patients undergoing ileocaecal resection or right hemicolectomy . These factors included age, gender, co-morbidity (diabetes & ischaemic heart disease IHD), smoking status, body mass index (BMI), statin medication, medical treatment for CD (steroids within one week prior to operation, 5-ASA within one week prior to operation, immuno-modulators within four weeks prior to operation, biologics within 12 weeks prior to operation), intra-abdominal abscess/pelvic collection, albumin, serum creatinine, haemoglobin, nutritional support (oral, enteral and parenteral nutrition) and ASA grade.

Also, surgeon and surgery-related factors were collected: urgency of surgery (urgent i.e. within 24, expedited i.e. within two weeks and elective), previous surgery in the area, details of surgeon in charge (trainee versus consultant, colorectal versus general surgeon), access to abdominal cavity (open, laparoscopic, or laparoscopic converted to open), extent of proximal resection (figure 1), details of anastomosis (type, configuration, instruments used), defunctioning/primary stoma, skin closure (suture or stapling), operation duration, and unplanned intraoperative adverse events (UIAEs) including injury to liver, gallbladder, duodenum, kidney, ureter, major blood vessels and bowel injury).

Outcome measures

The primary outcome measure was the overall postoperative complication rate classified according to the Clavian-Dindo scale (grade I to V). The secondary outcome measures were:

- Clinically suspected anastomotic leak defined as either i) gross anastomotic leakage proven radiologically or clinically or ii) the presence of an intraperitoneal (abdominal or pelvic) fluid collection on postoperative imaging.
- Surgical site infection (SSI) within 30 days defined according to the centers for disease control (CDC) criteria .
- Unplanned re-operation within 30 days
- Length of postoperative stay in hospital (LOS)

Inclusion Criteria

Adult patients undergoing right hemicolectomy or ileocaecal resection at a participating hospital during the study period, for CD pathology, via any operative approach and in both the elective and emergency settings, with or without primary anastomosis, performed by colo-rectal, general or trainee surgeons.

Exclusion Criteria:

- Right hemicolectomy or ileocaecal resection as part of a bigger procedure such as subtotal colectomy or pan-proctocolectomy
- Those in whom the distal colonic transaction point was beyond the splenic flexure
- Those undergoing additional upstream strictureoplasty or resection to treat concurrent small bowel disease more proximally during the same operation

Statistical analysis

Pearson's Chi square and Fisher's exact tests were applied for categorical variables in univariate analysis, while Mann-Whitney's test used for continuous variables. Continuous variables are reported by median and interquartile range (IQR). Univariate and multivariate

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regression models were used to assess the association between risk factors and outcome. For binary outcomes (e.g. complication yes/no), binary logistic regression modelling was used to produce odds ratios (OR). For continuous variables (e.g. LOS), normality was tested and linear regression modelling was used, with results presented as exponential transformations of the regression coefficients. Logarithmic transformation implemented when needed. Covariates included in regression models were those statistically significant in univariate analyses or those deemed important from clinical experience. Results for analyses of were presented with corresponding 95% confidence interval (CI). P-value less than 0.05 was considered significant. SPSS version 19 used for descriptive and univariate analyses while “R” used for multivariate analyses.

Results

Within the full audit cohort of 3041 patients, 375 operations were performed for CD patients in 151 centres around the world. The operations included in this study represent a subgroup of the main ESCP audit cohort (26).

Preoperative status

Patients' demographics and preoperative data are reported in table 1. Fourteen patients (3.7%) had an abnormal serum creatinine level preoperatively, 114 (30.4%) had albumin below normal levels (defined by local laboratories in the participating hospitals). Sixty-eight patients (18.1%) had a preoperative intra-abdominal abscess, however, only eighteen (4.8%) had their abscess drained preoperatively with a median interval between abscess drainage and surgery 29 days [IQR 37]. Seventy percent of patients (263/375) were on one or more

type of medical treatment (table 1). Sixty-six patients (17.8%) received a high steroid dose (defined as 20 mg or more preoperatively (11)).

Intraoperative details

Details of surgical procedures are shown in table 2. Colorectal specialists, in elective settings, did more than two thirds of the procedures. The proximal resection margin was 10-30 cm upstream from the ileocaecal valve in the majority of patients and through the caecum or ascending colon distally. A primary anastomosis was performed in 334/375 (89.1%) of the patients; of these 65.9% (220/334) were stapled. Side to side (215/334) stapled anastomoses was the most commonly used configurations usually in the form of extra-corporal anastomosis (105/334). Stomas were constructed in 46/375 (12.3%) of patients.

Postoperative course

One hundred-and twenty-six patients (33.6%) had one or more postoperative complications, of whom 22 (7.3%) had a complication requiring reoperation within 30 days (table 3). Median LOS was 7 days (IQR 5). The unplanned readmission rate was 5.3% (20/375).

Univariate Analysis

Postoperative complications were associated with parenteral nutrition, co-morbidity urgent/expedited operations and unplanned intraoperative adverse events (table 4). The Risk of re-operation increased in patients who received parenteral nutrition $p=0.14$ (OR 3.551 95% CI [1.216-10.370]) and stapled skin closure $p=0.023$ (OR 2.763 95% CI [1.115-6.842]). SSI correlated with low preoperative albumin $p=0.038$ (OR 0.507 95% CI [0.264-

0.973]), parenteral nutrition $p=0.01$ (OR 3.029 95% CI [1.263-7.267]), open access to abdominal cavity $p=0.03$ (OR 0.493 95% CI [0.257-0.943]) and stapled skin closure $p<0.001$ (OR 2.958 95% CI [1.525-5.737]).

Medical treatment was not associated with an increased risk of postoperative complications or re-operation even when this was investigated for each type of the above-mentioned drugs' categories and different surgical procedures.

Prolonged postoperative LOS (figure 2) correlated with parenteral nutrition ($p=0.002$), ASA grade 3&4, ($p<0.001$), urgent/expedited operations ($p<0.001$) and stoma construction ($p<0.001$).

As figure 3 shows, peak CRP level on third postoperative day correlated with any postoperative complication $p<0.01$ (OR 66.713 95 % CI [40.397-93.029]) and more specifically it correlated with postoperative anastomotic leak $p=0.029$ (OR 59.807 95 % CI [6.322-113.283]).

Multivariate analysis

After adjustment for other preoperative and intraoperative factors, parenteral nutrition, urgent/expedited operations and UIAEs were associated with increased risk of postoperative complications as reported in table 4.

Discussion

This study analysed data on patients with CD collected as part of the first ESCP international prospective audit. It provided baseline data for both demographics and surgical management across 151 centres in 37 different countries. The key findings were that

parenteral nutrition, urgent/expedited operations, and unplanned intraoperative adverse events were associated with higher risk of postoperative complications.

Timing of surgical intervention in CD is a crucial issue (27,28). Patients operated on in the acute setting are probably those with sepsis or intestinal obstruction, they might therefore have higher risk of postoperative complications. Attempts should be made to operate on CD patients in elective settings. This will necessitate a well planned preoperative optimization (8) to prevent deterioration of patients' general health. However more research on the nature of this, including timing and selection, is needed (28). Well-timed, well-optimised elective surgery can only be achieved in a setting of a close cooperation between IBD-surgeon and gastroenterologist.

Parenteral nutrition might reflect the severity of CD. Although disease severity and nutritional status were not collected as part of this audit, parenteral nutrition correlated with low levels of albumin and haemoglobin confirming that those patients were likely to be suffering from malnutrition. The evidence supporting preoperative optimization in patients with CD is increasing (27,16), including multi-model interventions based on detailed diagnostic imaging and close cooperation between dedicated IBD-surgeon and gastroenterologist (17).

Unplanned intraoperative adverse events increased the risk of postoperative complications. This is in line with a recent study (29) which showed that UIAEs were independently associated with increased 30-day mortality, 30-day morbidity and prolonged postoperative LOS. Quality improvement efforts should focus on prevention of these events, mitigation of harm after occurrence of event, and risk/severity-adjusted tracking and benchmarking. UIAEs defined as any deviation from the ideal intraoperative course occurring between skin

incision and skin closure (30). Table B in the supplementary material shows the details of UIAEs.

Other risk factors did not have significant impact on the outcome within this study.

Anastomotic type, site, configuration and instrumentation (type of staples devices and suture material) was not associated with any variation in postoperative outcome, but our study size is insufficient to be confident of this finding (table A in the supplementary material provides details of anastomotic technique). Preoperative medical treatment has been debated in the literature, with conflicting results. In this study, their use was not associated with improved or worse outcomes. Biologics dose, duration of treatment, drug bioavailability, and neutralising antibodies are essential factors that may influence postoperative outcome.

The key strengths of this study lie in its cross sectional and prospective nature which captured contemporaneous and unselected data from 151 sites internationally using a dedicated online system. Although the sample size was relatively low, this study still represents one of the most wide scale studies in the literature. Another limitation is the lack of details on other possible confounders, including disease phenotype, severity, preoperative nutritional screening, details of regimes used for nutritional support, duration of medical treatment prior to surgery, duration of postoperative thrombosis prophylaxis, and use of steroid stress dose. It must also be noted that this study design cannot ever provide irrefutable evidence on the impact of a particular variable; despite careful multivariable regression modelling we can never fully control for selection bias effects or the hidden confounders and interaction effects inherent in the complex decision making processes that underpin surgical care.

Our study identified that that parenteral nutrition, urgent/expedited operations, and unplanned intraoperative adverse events were associated with higher risk of postoperative complications in this population of patients undergoing ileo-caecal or right sided resections for Crohn's disease. These findings may highlight the need for enhanced cooperation and communication between members of the IBD multidisciplinary team to improve pathways for patients needing surgical intervention, which might in turn improve outcomes. There is certainly a need for further prospective research in this area; we need to establish the potential benefits bought by delaying urgent surgery where possible, optimising nutrition and undertaking planned surgery in a more controlled manner upon outcomes for patients.

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Table 1: Descriptive details of Preoperative medications in 375 CD patients

Age (median, IQR)		37 years, IQR 23
Gender: female n (%)		214/375 (57.1%)
Co-morbidity:	Diabetes Mellitus n (%) Ischaemic heart diseases n (%)	7/375 (1.9%) 10/375 (2.7%)
ASA:	ASA1 n (%) ASA2 n (%) ASA3 n (%) ASA4 n (%)	88/375 (23.5%) 239/375 (63.7%) 45/375 (12%) 3/375 (0.8%)
Preoperative albumin below normal limits		117 (31.2%)
Preoperative Haemoglobin (median, IQR)		12.8 g/dl, 2.2
Smoking:	Non-smoker n (%) Ex-smoker n (%) Current smoker n (%) Missing	219/375 (62.2%) 52/375 (14.8%). 81/375 (21.6%) 23/375 (6.1%)
Preoperative nutritional support	Parenteral nutrition Enteral nutrition. oral nutrition	32/375 (8.5%) 12/375 /3.2%) 28/375 (7.5%)
Body mass index (median, IQR)		22.9, 5.8
Medical treatment	Cholesterol lowering (Statin)	15/375 (4%)
	5-ASA agents	73/375 (19.7%)
	Mesalazin (Pentasa)	41/375 (11.1%)
	Mesalazin	23/375 (6.2%)
	sulfasalazin	9/375 (2.4%)
	Steroids	114/375 (30.7%)
	Prednisolon	88/375 (23.7%)
	Budesonid	15/375 (4%)
	Entocort	5/375 (1.3%)
	Hydrocortison	5/375 (1.3%)
	Dexamethason	1/375 (0.3%)
	Immuno-modulators	127/375 (34.2%)
	Azathioprine	97/375 (26.1%)

	6-Mercaptopurin	6/375 (3.2%)
	Methotrexate	10/375 (2.7%)
	Puri-Nethol	4/375 (1.1%)
	Cyclosporine	2/375 (0.5%)
	Biologics	82/375 (22.1%)
	Adalimumab	44/375 (11.9%)
	Infliximab	33/375 (8.9%)
	Vedolizumab	4/375 (1.1%)
	Certolizumab	1 /375 (0.3%)

IQR: interquartile range. ASA: America society of anaesthesiologist's physical status grading

Table 2 Details of surgery in 375 CD patients included in the ESCP prospective audit.

Timing of surgery	<ul style="list-style-type: none"> • Urgent (Emergency) within 24 hours: 54/375 (14.4%) • Expedited within two weeks: 49/375 (31.1%) • Elective (planned): 272/375 (72.1%)
Previous surgery in the area n (%) 253/375 (67.5%)	<ul style="list-style-type: none"> • One surgery 32/375 (8.5%) • Two surgeries 57/375 (15.2%) • Three surgeries 33/375 (8.8%)
Surgeon in charge n (%)	<ul style="list-style-type: none"> • Trainee general surgeon 23/375 (6.1%) • Consultant general surgeon 39/375 (10.4%) • Trainee colo-rectal surgeon 57/375 (15.2%) • Consultant colo-rectal surgeon 256/375 (68.3%)
Access to abdominal cavity n (%) Laparoscopy 219/375 (58.4%)	<ul style="list-style-type: none"> • Laparoscopy 177/375 (47.2%) • Laparoscopy converted to open via midline incision 40/375 (10.7%) • Laparoscopy converted to open via transvers incision 2/375 (0.5%)
Open 156/375 (41.6%)	<ul style="list-style-type: none"> • Open through midline incision 151/375 (40.3%) • Open through transvers incision 5/375 (1.3%)

Proximal resection margin from Caecum (figure 1)	<ul style="list-style-type: none"> • 0 cm from Caecum 18/375 (4.8%) • 10 cm from Caecum 90/375 (24%) • 20 cm from Caecum 104/375 (27.7%) • 30 cm from Caecum 63/375 (16.8%) • 40 cm from Cecum 81/375 (21.6%) • 50 cm or more from Caecum 13/375 (3.5%) • Not stated 6/375 (1.6%)
Distal resection margin (figure 1)	<ul style="list-style-type: none"> • Caecum 138/375 (36.8%) • Mid-colon ascendance 128/375 (34.1%) • Oral for hepatic flexure 26/375 (6.9%) • Anal for hepatic flexure 33/375 (8.8%) • Mid-colon transverse 33/375 (8.8%) • Oral for splenic flexure 6/375 (1.6%) • Splenic flexure 2/375 (0.5%) • Not stated 9/375 (2.4%)
Unplanned intra-operative events n (%): 56/371 (15.1%)	<ul style="list-style-type: none"> • Bleeding 24/375 (6.4%) • Duodenum injury 1/375 (0.3%) • Renal injury 1/375 (0.3%) • Enterotomy 6/375 (1.6%) • Injury to other organs 1/375 (0.3%) • Revision of anastomosis 4/375 (1.1%) • Extensive intra-abdominal adhesion 6/375 (1.6%) • Other events 16/375 (4.3%) • Ureteric, liver, gallbladder vascular injury 0%
Unexpected Intra-abdominal finding related to CD n (%): 279/375 (74.4%)	<ul style="list-style-type: none"> • Intra-abdominal abscess 33/375 (8.8%) • Enteric fistula 123/375: (30.4%) <ul style="list-style-type: none"> o 59//375 (15.7%) entero-colic o 35/375 (9.3%) entero-enteric o 12/375 (3.2%) entero-vesicle o 17/375 (4.5%) entero-cutaneous fistula • Small bowel obstruction 123/375(32.8%)
Skin closure	<ul style="list-style-type: none"> • Suture 229/375 (61.1%) • Stapled 143/375 (38.1%) • Not stated 3/375 (0.8%)
Duration of operation	Median 128 minutes (IQR 59).

Table 3: Descriptive details of 30-day postoperative outcome in 375 CD patients

Admission to critical care unit		70/375 (18.7%)
	Planned from the theatre	66/375 (17.6%)
	Unplanned from the theatre	2/375 (0.5%)
	Unplanned from the ward	2/375 (0.5%)
Postoperative complications classified according to Clavien-Dindo classifications	Any complication	126/375 (33.6%)
	Grade I	39/375 (10.4%)
	Grade II	60/375 (16%)
	Grade III	33/375 (8.8%)
	Grade IV	5/375 (1.3%)
	Grade V	None
Specific complications	Overt anastomotic leak or intra-abdominal pelvic collection	33/375 (8.8%)
	Re-operation	22/375 (5.9%)
	Surgical site infection	42/375 (11.2%)
Re-admission		20/375 (5.3%)

Table 4: Univariate and multivariate logistic regression analyses showing risk factors for postoperative complication in patients with Crohn's disease undergoing right hemicolectomy or ileo-caecal resection.

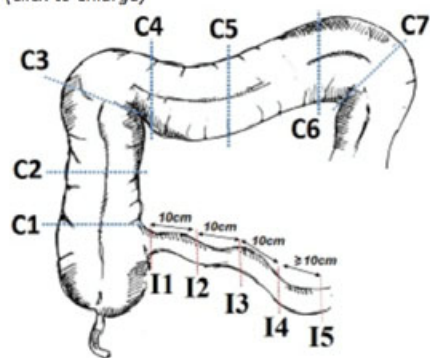
Co-variates in the model*		Univariate analysis			Multivariate analysis		
		<i>Odds Ratio</i>	<i>95% CI</i>	<i>P-value</i>	<i>Odds Ratio</i>	<i>95% CI</i>	<i>P-value</i>
Age		1.02	[1-1.03]	0.0274	1.01	[0.99-1.02]	0.4383
Gender	Female	1.23	[0.78-1.94]	0.375	0.89	[0.55-1.45]	0.6386
	Male						
ASA Grade	Low grade (I & II) High grade (II & IV)	1.58	[0.84-2.98]	0.152	1.18	[0.57-2.46]	0.6505
Smoking Status	Non-smoker	1.49	[0.93-2.38]	0.0989	1.29	[0.78-2.11]	0.3172
	Ex-/current smoker						
Co-morbidity	No Yes	3.67	[1.2-11.1]	0.0212	2.67	[0.81-8.83]	0.1075
Preoperative Haemoglobin		1.03	[0.9-1.18]	0.642	1.09	[0.94-1.27]	0.2363
Low Albumin	No Yes	1.02	[0.65-1.61]	0.932	1.29	[0.77-2.14]	0.3347
Biologics:	No Yes	0.886	[0.5-1.58]	0.68	0.92	[0.51-1.67]	0.7919
Parenteral nutrition	No Yes	2.36	[1.1-4.97]	0.0234	2.85	[1.20-6.74]	0.0173
Urgency of surgery:	Elective Urgent/expedited	1.96	[1.2-3.22]	0.007	2	[1.13-3.55]	0.018
Surgeon in charge:	General Colorectal	0.809	[0.45-1.45]	0.477	0.92	[0.47-1.83]	0.819
Access to abdomen:	Open Intended laparoscopic	0.824	[0.52-1.29]	0.4	1.19	[0.68-2.08]	0.5421

Defunctioning/primary stoma:	No Yes	0.901	[0.45-1.79]	0.766	0.98	[0.45-2.12]	0.9594
Skin closure:	Suture Stapling	1.61	[1-2.56]	0.0459	1.27	[0.76-2.12]	0.3654
UIAE	No Yes	2.51	[1.4-4.55]	0.00239	2.31	[1.20-4.45]	0.0123

*Only clinically important co-variables are shown in this table.

UIAEs: unplanned intraoperative adverse events:

2.2 Actual operation performed
(select nearest approximate proximal and distal margins)
(click to enlarge)



a. If Other, please specify

Proximal

- ☐ I1
☐ I2
☐ I3
☐ I4
☐ I5
☐ Other

Distal

- ☐ C1
☐ C2
☐ C3
☐ C4
☐ C5
☐ C6
☐ C7
☐ Other

Figure 1 A screen shot of the figure used in data collection process to map the extent of resection. The proximal resection margin (I) while distal resection margin ©.

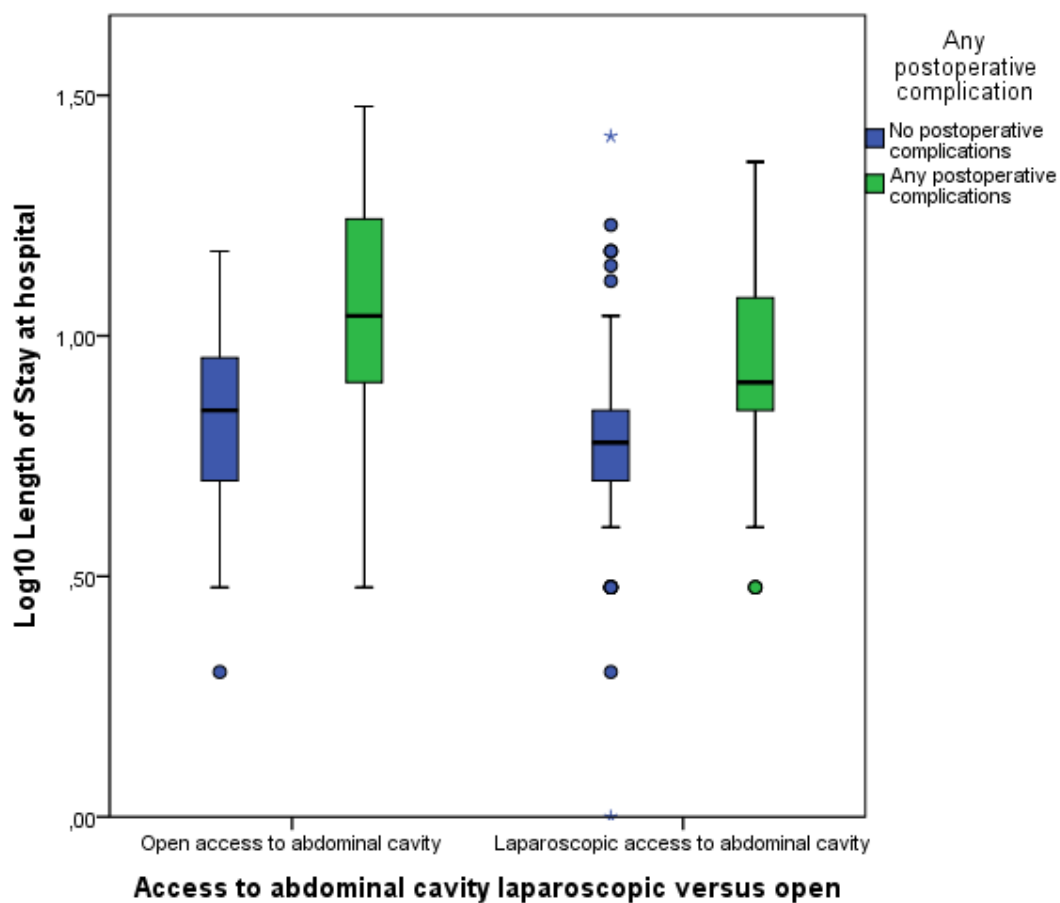


Figure 2 Showing a longer length of postoperative stay (LOS) for patients who were operated via open access to abdominal cavity compared to those operated via laparoscopic access.

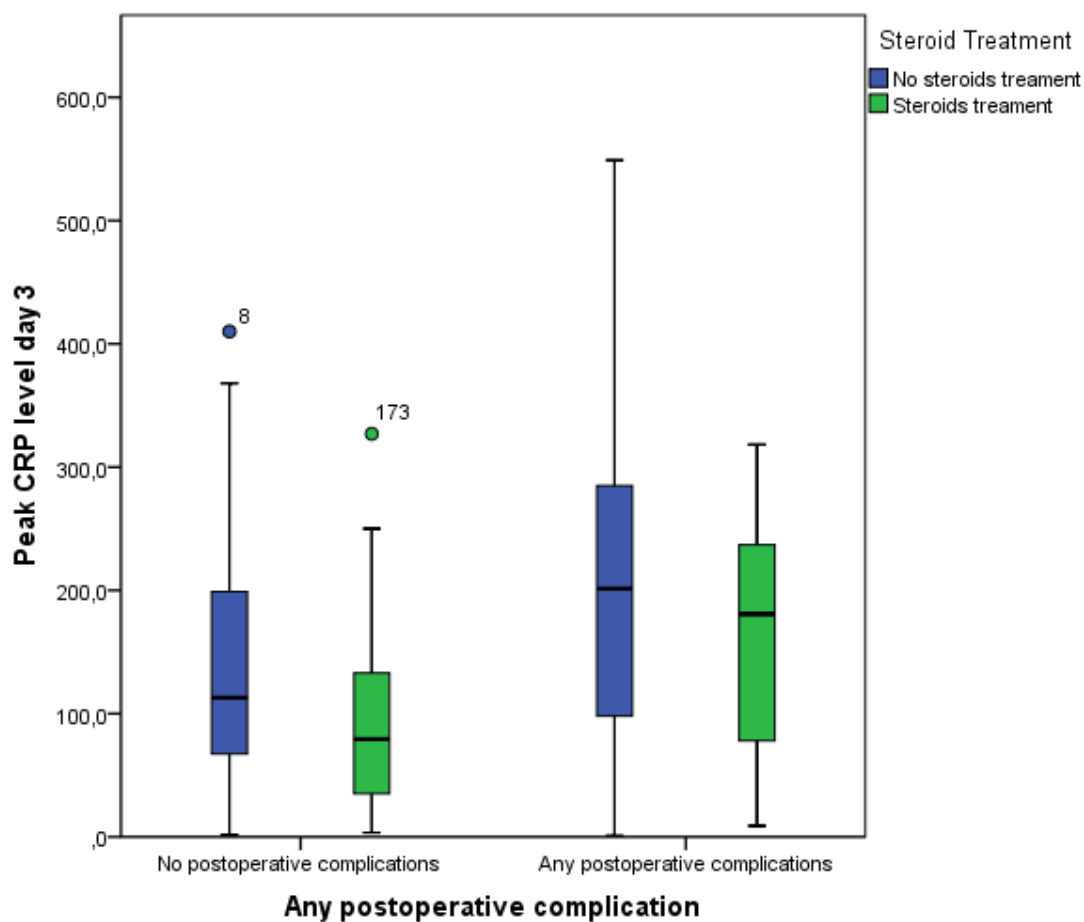


Figure 3 Postoperative complications and CRP peak level within the first 3 postoperative days. Note that treatment with corticosteroids depressed CRP elevation in both groups.

ONLINE-ONLY SUPPORTING INFORMATION

APPENDIX

TABLES A AND B